M E M O R A N D U M

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation Research
Office of Blood Research and Review

To:	BLA STN 125487/0 and Pracht, Leigh, OBRR/DBA/RPMB/
From:	Andrey Sarafanov, PhD, OBRR/DH/LH
Applicant:	Biogen Idec, Inc.
Product:	Antihemophilic Factor (Recombinant), Fc Fusion Protein (Recombinant Coagulation Factor VIII-Fc Fusion Protein, [ELOCTATE])
Subject:	Chemistry, Manufacturing and Controls Review (Analytical Methods for Drug Substance & and section 3.2.P – Drug Product, except section 3.2.P.8)
Through:	Mark Weinstein, PhD, OBRR/IOD
	Basil Golding, MD, Director, DH/OBRR
CC:	Tim Lee and Nancy Kirschbaum

EXECUTIVE SUMMARY

This memorandum summarizes the review of product-related information in an original Biologics License Application (BLA) under STN 125487 submitted by Biogen Idec, Inc. (Biogen) for Coagulation Factor VIII (Recombinant), Fc Fusion Protein (rFVIII-Fc). I have reviewed information in the submission Module 3 (Quality) sections 3.2.S.4.2 and 3.2.S.4.3 (Drug Substance, validation of analytical methods), and 3.2.P (Drug Product) except section 3.2.P.8. During the review, information requests (IRs) were sent to the Applicant, who provided the requested information and addressed the concerns in a satisfactory way. Based on the totality of this information, I found the BLA to be approvable.

REVIEW SUMMARY

3.2.S.4.2 & 3.2.S.4.3, ASSAY METHODOLY AND VALIDATION FOR DRUG SUBSTANCE

[b(4)]

3 Pages determined to be not releasable: b(4)

Upon initial review of the submission, FDA requested to provide additional information for the method robustness. In Amendment 12 (August 07, 2013), Biogen provided this information. This and the above information were reviewed by the Division of Biological Standards and Quality Control (DBSQC). In their collective memo (October 9, 2013), it was concluded that the method was validated adequately for the potency ---b(4)----- testing of –b(4)---- all seven DP strengths.

- In Amendment 30 (received on November 27, 2013), Biogen provided additional documentation describing validation of the VIII potency assay for -b(4)-- DP. This information was found to be acceptable as reviewed under Communication with the Applicant, Question 1.

COMPARISON OF CHROMOGENIC AND CLOTTING ASSAYS FOR THE TESTING OF rFVIII-FC

In Amendment 7 (May 31, 2013), Biogen provided information about comparison of the clotting and chromogenic assays. During the clinical development, the DP potency assignment evolved from an aPTT assay calibrated to the –b(4)---------- ----------
---

---.

Comparative testing of all DP strengths showed a linear correlation between the assays. ----b(4)-- ----------
---

--b(4)-- ----------

---. As a result of both DP and clinical studies testing, Biogen concluded that there is a high correlation between the results of aPTT and chromogenic assays in determining activity of rFVIII-Fc.

Reviewer Comment

RFVIII-Fc activity in clinical samples was measured by the chromogenic assay (section 5.3.1.4). In section 3.2.S.3.1 (p. 39), it is stated that "The two assays (i.e. chromogenic and aPTT) are considered to be equivalent for the assessment of rFVIII-Fc activity" (also, section 3.2.S.2.6). As FDA stated in the face-to face meeting on August 2, 2012 (question 9, BLA section 1.6.3, p. 21), "please be advised that FDA decision regarding an appropriate potency assay will be made during BLA review…" The aPTT test to characterize potency of rFVIII-Fc was recommended to compare with the chromogenic test. During initial review of the submission, FDA requested to perform all comparative testing between one-stage (clotting, aPTT) and chromogenic assay , including patient monitoring and product release.

--b(4)----------
----b(4)-- ----------

---

2 Pages determined to be not releasable: b(4)

--b(4)--- ----------

----------**b(4)**----------
---b(4)---- ----------

3.2.P DRUG PRODUCT (rFVIII-Fc)

3.2.P.1 DESCRIPTION AND COMPOSITION OF OHE DRUG PRODUCT

The rFVIII-Fc DP is a sterile lyophilized powder aseptically filled in vials in nominal strengths of 250, 500, 750, 1000, 1500, 2000 and 3000 IU/vial. The composition of the solution prior to its lyophilization is the same for all dosage strengths; only the quantity of rFVIII-Fc varies. The powder is reconstituted with 3 mL of sterile water for injection (SWFI) supplied in a sterile pre-filled syringe. When reconstituted, the DP contains the following excipients: -b(4)- sucrose (-b(4)---------- NaCl (----b(4)---------- L-histidine (--b(4)---------- $CaCl_2$ (--b(4)---------- polysorbate-20 –b(4)----------). . These ingredients are specified in --b(4)----------. The container closure consists of –b(4)---------- glass vial closed with a ---b(4)---------- stopper and sealed with a 20 mm aluminum flip-off crimp seal, which color varies depending on the dosage strength.

3.2.P.2 PHARMACEUTICAL DEVELOPMENT

1-2. Drug Product and its Components

During the DP development, the targeted DP composition was aimed to ensure: i) long-term storage stability at 2 to 8 °C, ii) compounding aimed DP strengths (250-3000 IU/vial) and iii) aimed stability of reconstituted DP. The DP development was completed through two stages of clinical development. Preclinical and Phase 1/2a clinical studies were conducted using a ----b(4)----------, and the Phase III studies were conducted using the lyophilized DP. Between these DP variants, the excipients composition was slightly different. Studies showed comparability between the –b(4)------- and lyophilized DP versions (3.2.P.2.3).

During the DP formulation development, the optimal concentrations of excipients were defined. Initially, the concentrations of NaCl, $CaCl_2$ and PS-20 were optimized to maintain rFVIII-Fc solubility, integrity and stability. The formulation was further optimized during development of the –b(4)------- DP; in particular, -b(4)-- was introduced as a –b(4)---------. During development of the lyophilized DP formulation, the excipients composition and concentrations were further optimized to stabilize the DP during the lyophilization, storage and upon the reconstitution. During this study, the parameters of –b(4)---------- and Potency (by

aPTT) were controlled. The levels of NaCl, sucrose, $CaCl_2$ and PS-20 were further optimized, ------b(4)----------

During these studies, robustness of the formulation process was also evaluated by testing variations in the excipients compositions. It was found that the DP is robust across the ---b(4)----------. It was established that an overage of b(4) for the DP vials of 500-3000 IU strengths and b(4) for 250 IU strength is needed to ensure that the nominal potency is achieved per the label claims to compensate the potency loss during the DP manufacturing. Finally, it was established that physico-chemical and biological properties of the DP are essentially the same as those of DS.

3. Manufacturing Process Development

As the DP is produced at different strengths, its formulation is based on utilizing a –b(4)----- system of –b(4)-- composition. ---b(4)----------

---b(4)--- ----------

--b(4)-- ----------

--b(4)-- ----------

4. Container Closure System

--b(4)-- ----------

container closure integrity over time (3.2.P.8.1). Compatibility of the stopper with the reconstituted DP was demonstrated (3.2.P.2.6). Extractable and leachable data are provided in Section 3.2.P.7. After the lyophilization process is complete, the stoppered vials are sealed with 20 mm aluminum seals with a --b(4)-------- flip-off cap of various colors depending on the DP dosage.

5. Microbiological Attributes

Sterility testing is performed as part of release of the DP (3.2.P.5.2.15). Container Closure Integrity testing studies (3.2.P.5.2.16) is performed in lieu of sterility testing (3.2.P.8.3), and reviewed by a DMPQ reviewer.

6. Compatibility

In-use stability and compatibility of the DP with administrations materials was demonstrated after a ---b(4)----------. The following parameters were assessed: i) --b(4)--- ---------- The results met the acceptance criteria that indicated suitability of the system for the intended purpose.

3.2.P.3 MANUFACTURE

1. Manufacturers.

- DP manufacturing is performed by ----------b(4)----------
- DP quality testing is performed by i) Biogen at 14 Cambridge Center Cambridge, MA 02142; at ---b(4)----------.
- --b(4)---------- ----------.
- DP labeling and packaging is performed by i) Biogen –b(4)-- ----------
- Product warehousing is performed –b(4)-- ----------
- ---b(4)---- ----------

2. Batch Formula

The DP is produced at seven strengths (250-3000 IU/vial) having the same excipients content as listed above. This is achieved by balancing the concentrations of excipients during the formulation of liquid DP. The quality of the excipients and the diluent (SWFI) corresponds to those described in relevant sections of USP-NF, Ph. Eur., JP compendia.

3. Manufacturing Process and Controls

The process of DP manufacture consists of following steps:

1. -----b(4)----------
2. -----b(4)----------
3. -----b(4)----------
4. -----b(4)----------
5. -----b(4)----------

6. -----b(4)----------
7. -----b(4)----------
8. -----b(4)----------
9. -----b(4)----------
10. -----b(4)----------
11. -----b(4)----------

--b(4)---------- ----------

--b(4)-- ----------

--b(4)-- ----------

--b(4)-- ----------

--b(4)--- ----------

--b(4)--- ----------

--b(4)-- ----------

---

4. Controls of Critical Steps and Intermediates

The controls described are relevant to the process at the –b(4)- facility. The criticality of process steps was determined through a risk analysis of the DP manufacturing process. Process inputs and outputs were defined and then assessed based on their potential impact on product quality, process yields, and likelihood of occurrence. The section includes definitions for the control limits of the process and lists the in-process controls, in-process tests and key-controlled parameters. Critical controls of the manufacturing process include those relevant to the process steps reviewed under a previous paragraph (#3).

5. Process Validation and/or Evaluation

The manufacturing process validation approach is consistent with an agreement reached during a Type C meeting of CBER with Biogen on September 7, 2011 (CRMTS # 8063). The process validation was conducted at the –b(4)- facility to demonstrate that the manufacturing process consistently produces product meeting predefined quality attributes. The section describes specific subsets of validated critical parameters of the processes, i. e. –b(4)---------- steps. The –b(4)----- process is designed to be similar for all strengths and their downstream is the same. Hence, the manufacturing process for each of the seven dosage strengths was considered equivalent. Three consecutive DP ***validation lots*** were manufactured in 2012 for each of highest and lowest commercial dose and placed on stability. These lots are the following: -b(4)---------- (250 IU/vial); and –b(4)---------- (3000 IU/vial). Other DP lots of all strengths produced previously (in 2011) were classified as ***conformance lots***. These lots are the following: -b(4)---- (250 IU/vial), --b(4)----- (500 IU/vial), --b(4)------- (750 IU/vial), -b(4)---- (1000 IU/via), -b(4)---- (1500 IU/vial), -b(4)---- (2000 IU/vial) and –b(4)----- (3000 IU/vial). For these lots, the results were retrospectively compared to those for the validation.

Reviewer Comment.

Although Section 3.2.P.3.5 does not contain results from the lots or a key conclusion that the process had been validated, these results are listed in section 3.2.P.5.4. These results met the release specification; therefore, the manufacturing process can be considered validated.

3.2.P.4 CONTROL OF EXCIPIENTS

1-6. Specifications and Analytical Procedures

All excipients used in the manufacture of rFVIII-Fc DP are manufactured according to compendial monographs. All excipients are of a compendial grade (USP, Ph. Eur, and/or JP); justification of their specifications, therefore, is not applicable. No excipients of human or animal origin are used. Upon receiving the excipients from the vendors, their testing is performed in the following assays.

- Sucrose --b(4)----------
- L-Histidine --b(4)----------
- Calcium Chloride --b(4)----------
- Polysorbate 20 --b(4)----------
- Water For Injection --b(4)----------

Other analytical procedures used are to control formulation –b(4)--------, and include –b(4)---------- testing. Validation of these procedures is not applicable.

3.2.P.5 CONTROL OF DRUG PRODUCT

3.2.P.5.1 Specifications

The specifications are established in accordance with ICH Q6B. With the exception of chromogenic activity per vial and –b(4)-------, specifications for all the vial strengths are the same.

Table 2. Release and stability specifications for lyophilized Drug Product (all vial strengths)

Attribute	Reference to Method	Proposed Commercial Acceptance Criteria	
		Release	Stability
General Characteristics			
Appearance, Lyophilized	3.2.P.5.2.1	White to Off White Cake to Powder	White to Off White Cake to Powder
Reconstitution Time	3.2.P.5.2.2	(b) (4)	
Residual Moisture	3.2.P.5.2.3		
Appearance of the Reconstituted Solution	3.2.P.5.2.4		
(b) (4)	3.2.P.5.2.5		
	3.2.P.5.2.6		
Calcium (b) (4)	3.2.P.5.2.7		
Polysorbate 20	3.2.P.5.2.8		
Physicochemical Properties			
(b) (4)	3.2.P.5.2.10	(b) (4)	
Identity			
(b) (4)	3.2.P.5.2.11	(b) (4)	
	3.2.P.5.2.12		

Attribute	Reference to Method	Proposed Commercial Acceptance Criteria	
		Release	Stability
Quantity			
Protein Concentration (b) (4)	3.2.P.5.2.9	(b) (4)	
Biological Activity			
Chromogenic Activity Assay (b) (4)	3.2.P.5.2.11	(b) (4)	
Chromogenic Activity Assay (activity/vial)	3.2.P.5.2.11		
Purity and Impurities			
(b) (4)	3.2.P.5.2.12	(b) (4)	
(b) (4)	3.2.P.5.2.13		
Safety			
Endotoxin	3.2.P.5.2.14		

Attribute	Reference to Method	Proposed Commercial Acceptance Criteria	
		Release	Stability
Sterility	3.2.P.5.2.15	No Growth	Not Tested
Container Closure Integrity	3.2.P.5.2.16	Not Tested	Pass
Particulate Matter (b) (4) (b) (4)	3.2.P.5.2.17	(b) (4)	

3.2.P.5.2 and 3.2.P.5.3 Assay Methodology and Validation for Drug Product

Table 3. Analytical procedures used to test Drug Product

Attribute	Test Method	Descript.	Validation
General	Appearance	3.2.P.5.2.1	3.2.P.5.3.1
General	Reconstitution Time	3.2.P.5.2.2	3.2.P.5.3.2
General	Residual Moisture	3.2.P.5.2.3	3.2.P.5.3.3
General	Appearance of the Reconst. Product	3.2.P.5.2.4	3.2.P.5.3.4
General	---b(4)-------	3.2.P.5.2.5	3.2.P.5.3.5
General	---b(4)-------	3.2.P.5.2.6	3.2.P.5.3.6
General	Calcium	3.2.P.5.2.7	3.2.P.5.3.7
General	Polysorbate 20	3.2.P.5.2.8	3.2.P.5.3.8
Quantity	---b(4)-------	3.2.P.5.2.9	3.2.P.5.3.9
Physicochemical Properties	---b(4)-------	3.2.P.5.2.10	3.2.P.5.3.10
---b(4)- and Biol. Activity	Chromogenic Activity Assay	3.2.P.5.2.11	3.2.P.5.3.11
Identity, Purity and Impur.	---b(4)-------	3.2.P.5.2.12	3.2.P.5.3.12
Purity and Impurities	---b(4)-------	3.2.P.5.2.13	3.2.P.5.3.13
Safety	Endotoxin	3.2.P.5.2.14	3.2.P.5.3.14
Safety	Sterility	3.2.P.5.2.15	3.2.P.5.3.15
Safety	Container Closure Integrity	3.2.P.5.2.16	3.2.P.5.3.16
Safety	Particulates	3.2.P.5.2.17	3.2.P.5.3.17

Reviewer Comment

In the electronic form of the Application Content, sections 3.2.P.5.2.9 and 3.2.P.5.3.9 are mistakenly named as –b(4)----------), and section 3.2.P.5.2.10 is mistakenly named as Coagulation Assay (aPTT). At the same time, these sections actually describe procedures listed in the above table (--b(4)----------, respectively). On April 10, 2014, Biogen was sent a request to correct the issues and update the electronic file (Communication with the Applicant, Question 7).

1. Appearance (Lyophilized Drug Product)

DP sample is visually inspected for color of the lyophilized cake under ambient light on/against a white background. Because of the method is compendial, its validation was not performed.

2. Reconstitution Time

To a DP vial, 3.0 mL of the solvent, sterile water for injection (SWFI), is added, and the vial is gently swirled and inverted. The amount of time for the powder dissolves is assessed visually. Validation was performed by determination of precision in regard of specified reconstitution time of –b(4)----. In this study, DP with strengths of 250, 1000 and 3000 IU/vial (-b(4)------ per strength) were used. The average reconstitution time was about –b(4)-- with average –b(4)--------- By this, the method was considered as validated.

3. Residual Moisture

------b(4)-- --

Upon initial review of the submission, FDA requested description of some technical details of the assay. In Amendment 12 (July 07, 2013), Biogen provided this information.

> <u>Reviwer Comment</u>
> Considering the criticality of the Residual Moisture parameter for stability of the DP, suitability of the validated method to measure the moisture parameter should also be assessed by testing comparability of this method with another method, which is well-established, in particular, such as Karl Fisher titration method (Fischer, Karl (1935) Angew. Chem. 48 (26): 394-396) . A request to perform such a study was sent to the Applicant and addressed appropriately (Communication with the Applicant, Question 2).

4. Appearance of the Reconstituted Solution

An aliquot of reconstituted DP is visually inspected for color, clarity, and the presence of visible particles as described above for DS (3.2.S.4.2.1). The method is consistent with compendial requirements (----b(4)----------------------------------- therefore, its validation is not required. Biogen performed verification of the method and considered it suitable for the testing of DP.

5. –b(4)--------------------------------

-------------b(4)--------------------------------------- --
----

6. –b(4)------

--b(4)-- --

----

7. Calcium –b(4)----

---b(4)-- ---

-- --

b(4)-- ----------

Reviwer Comment

Upon initial review of the submission, FDA (DBSQC) requested additional information for the assay validation, including the SOP, a revision of the assay range, and data to show linearity and parallelism of the assay. The response was provided in Amendment 12 (August 7, 2013) and found to be acceptable.

8. Polysorbate-20 Assay

The concentration of Polysorbate-20 (PS-20) in the DP is determined by ----b(4)-- ----------
---

Reviwer Comment

Upon initial review of the submission, FDA (DBSQC) requested an SOP for the assay. In Amendment 12 (July 07, 2013), Biogen provided this document. Also, FDA requested Biogen to provide a representative ----b(4)---- of the analysis that was not presented in the original submission. In the response, Biogen provided these data (Communication with the Applicant, Question 4).

9. -----b(4)----------

-----b(4)---------- ----------

---.

Reviwer Comment

---b(4)--- ----------

---

10. ----b(4)----------

----b(4)---- ----------

11. Chromogenic Potency Assay

The method principle is described in review of a relevant section for b(4). Similarly to that for b(4) Biogen stated that method validation is not required since the assay is compendial (Ph. Eur), and performed only assessment of the methods suitability for the testing of DP. FDA still requested to validate the method in a complete way and Biogen provided such data in Amendment 7 (May 31, 2013). The method was validated for ----b(4)---- DP in acceptable way, as reviewed in a relevant section for ---b(4)---.

12. ----b(4)----------

----b(4)-- ----------

13. ---b(4)----------

----b(4)-- ----------

---b(4)-- ----------

----b(4)--- ----------
----

14. Endotoxin

----b(4)-- ----------

----

15. Sterility

---b(4)-- ----------

Reviwer Comment

--b(4)-- ----------
----------.

16. Container Closure Integrity

---b(4)-- ----------

----

17. Particulates

----b(4)-- ----------

3.2.P.5.4 Batch Analyses

This section provides data for release test results for –b(4)- of rFVIII-Fc DP manufactured at –b(4)----------
---------- lots of DP manufactured at –b(4)- facility and b(4) lots of DP manufactured at –b(4)-- facility. Among these lots, there are lots used for manufacturing process validation and conformance.

Validation lots include three consecutive lots for each of highest and lowest commercial doses. These lots were manufactured in 2012 and are the following: ----b(4)--- ----------
----

Conformance lots were produced in 2011 and include lots of all strengths. The results of these lots were used for retrospective qualification of the DP manufacturing process. These conformance lots are the following:

--------b(4)-- ----------

3.2.P.5.5. Characterization of Impurities

----b(4)-- ----------

3.2.P.5.6. Justification of Specifications

The DP release specifications (3.2.P.5.1) were developed consistent with ICH Q6B, *"Specifications - Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products."*

1. Critical Quality Attribute Evaluation

1. As a basis for establishing the specifications, risk assessment was conducted and a testing strategy was developed. The risk assessment (3.2.S.4.5) included evaluation and scoring of the impact of each product quality attribute on the DP efficacy and safety. In this study, a quality attribute (QA) was designated as critical (CQA) if its combined score was equal to or exceeded a preset criterion. Only the attributes that are unique to DP (or that can change during DP manufacturing) were assessed. Except for the ----b(4)--- ---------- (described in Section3.2.P.5.6.4), all the critical quality activities (CQAs) were included in the proposed DP specifications (3.2.P.5.1). For each specification parameter, the data presented (tabulated) show the impact and uncertainty scores, preset criterion, CQA or non-CQA qualification, testing strategy and test method.

2. Specification Summary

From the attributes evaluated in the –b(4)-- risk assessment for the DP, a subset of tests was proposed as its release and stability tests, described in section 3.2.P.5.2. Except for FVIII activity and –b(4)---------, the specifications developed are the same for all the DP strengths.

3-4. Justification of Release and Stability Specifications

According to ICH Q6B, the release tests were designed to assess the physical, chemical and biological integrity and the safety of DP by measuring attributes of: general characteristics, product identity, quantity, biological activity, purity, product-related impurities and contaminants. Final evaluation of CQA was performed based on the –b(4)- risk assessment, clinical manufacturing experience, clinical DP lot data, real-time and accelerated stability studies and process characterization results. The acceptance criteria for release testing were established based on the combination of manufacturing experience, test methods capability (limits of quantification, precision *etc*), developmental and stability studies, and regulatory guidelines. The section contains discussions on each specification parameter, including those not tested at the DP release (---b(4)----------). The non-testing of the latter parameters was justified by the following: i) –b(4)--- -----
---

3.2.P.6 REFERENCE MATERIALS

The reference standard used for testing the DP was the same as that for testing the DS.

3.2.P.7 CONTAINER CLOSURE SYSTEM

All DP strengths use the same container closure system. The DP is lyophilized in ---b(4)---------- glass vial, which is in accordance with –b(4)---------- requirements. The manufacturers are -b(4)---------- which authorization letters referring to the respective Drug Master Files (DMFs) are provided. The vial is closed with a 20 mm –b(4)----- elastomer stopper, ---b(4)---------- on the product contact and top sides, ----------b(4)----------. The stopper is compliant with ---b(4)----------. The manufacturer of the stopper is ----b(4)----------), which authorization letter referring to the respective DMFs is provided. After the lyophilization process is complete, the stoppered vials are sealed with 20 mm aluminum seals with a -b(4)---------- flip-off cap of various colors dependent on the vial strength. The manufacturer of the seal is --b(4)----------. The DP kit also includes a vial adapter transfer device for the reconstitution. The drawing of the container closure system is presented in Appendices A-D.

----b(4)-- ----------

---b(4)----------

---b(4)-- ----------

----b(4)----------

--b(4)--- ----------.

---b(4)----------

---b(4)--- ----------

Overall, the levels of extractables and leachables from the container closure components showed that the vial and stopper are suitable for use as a primary container closure system for the DP. Additionally, the long-term and accelerated stability profile of the DP stored in this container closure system demonstrated that the few extractable and leachable substances found do not have an impact on the overall the stability of the rFVIII-Fc DP (Section 3.2.P.8.1).

Validation of testing of container closure integrity is reviewed by our colleagues from DMPQ.

3.2.P.8 STABILITY

Stability of rFVIII-Fc was reviewed by Dr. Ze Peng (OBRR/DH).

3.2.P DRUG PRODUCT (DILUENT)

3.2.P.1 DESCRIPTION AND COMPOSITION OF OHE DRUG PRODUCT

The lyophilized rFVIII-Fc diluent represents Sterile Water for Injection (SWFI) supplemented in a pre-filled syringe (3 mL). The container closure system consists of a –b(4)-----glass barrel, --b(4)------ stopper and a closure system composed of a tip cap with and a tamper-evident seal.

3.2.P.2 PHARMACEUTICAL DEVELOPMENT

The methods chosen to ensure the quality, purity, and safety of the SWFI pre-filled syringes are based on the ---b(4)---------- ----------. The process validation for the SWFI pre-filled syringes involved a ---b(4)--- ---------- ----------. All results available so far reveal a satisfactory stability profile for the product.

3.2.P.3 MANUFACTURE

---b(4)-- ----------.

3.2.P.4 CONTROL OF EXCIPIENTS

Not applicable.

3.2.P.5 CONTROL OF DRUG PRODUCT

Product specifications includes such parameters as Appearance of Solution/Foreign insoluble matter, --b(4)---- ---------- Bacterial Endotoxins and Sterility. The respective testing methodology is designed to fully comply with current USP-NF, Ph. Eur. and JP. Relevant analytical procedures are listed and their validation (verification) is referred to DMF –b(4)----.

3.2.P.6 REFERENCE STANDARDS

As respective standards for the assays, pharmacopeial substances are used.

3.2.P.7 CONTAINER CLOSURE SYSTEM

Syringes are produced from –b(4)---- glass, ----------b(4)----------). Stopper is manufactured from –b(4)----- rubber (--b(4)---------- ----------. The closure system is composed of a tip cap with a Luer lock and a tamper-evident seal, and supplied by ----b(4)----------. Additional details are provided in DMF #-b(4)--- Validation of testing of the container closure integrity is reviewed by our colleagues from DMPQ.

3.2.P.8 STABILITY

Stability of the diluent for rFVIII-Fc was reviewed by Dr. Ze Peng (OBRR/DH.

COMMUNICATION WITH THE APPLICANT FOR ADDITIONAL INFORMATION

On September 11, 2013, an Information Request was sent to Biogen, and responded on November 27, 2013 (Amendment 30) as follows.

Question 1 (numbered as #11 in the correspondence)
Please provide a study report describing the complete validation of the commercial Factor VIII potency assay, to include testing of multiple commercial ---b(4)---------- drug product lots.

Response
Biogen provided data of two studies to validate the method for Factor VIII potency (chromogenic assay): a study consistent with ICH Q2, and an additional study to assess the Parallelism and Linearity of the method for –b(4)-- DP relatively the 8th WHO IS for FVIII.

For the first study, the information was previously was submitted to FDA in Amendment 10. In the present submission, Biogen referred to that amendment and provided the data summary. The parameters assessed included Accuracy, Precision (Repeatability, Intermediate Precision and Reproducibility), Assay Range/Linearity, and Specificity. The results met the acceptance criteria, thus the method was considered validated.

In the second study, the DP lots of 250 and 3000 IU strengths –b(4)------- were evaluated for Parallelism and Linearity across a range of the samples dilutions of –b(4)----- relatively 8th WHO IS for FVIII. The results were found to be acceptable as met the acceptance criteria.

Reviewer Comment
The information for validation of the potency assay (first study) was reviewed by the Division of Biological Standards and Quality Control (DBSQC). In a collective memo (October 9, 2013), the reviewers concluded that the method was validated adequately for the all seven current DP strengths -b(4)-------. For the second (additional) study, assessment of Linearity and Parallelism of the method for –b(4)---- DP, the information provided is acceptable.

Question 2 (numbered as #12 in the correspondence)
Please provide complete validation of the –b(4)---------- test against the accepted, compendial -b(4)------- test to cover the shelf life specification and all dosage strengths.

Response
Biogen provided data for validation of the –b(4)---------- test against –b(4)--------- test using the 250 IU and 3000 IU DP (-b(4)- lots), which –b(4)--- all dosage strengths. In the study, specific amounts of ---b(4)----------. The parameters studied were Linearity, Relative Accuracy and Relative Precision.

---b(4)-- ----------

Reviewer Comment
The response is acceptable.

Question 3 (numbered as #13 in the correspondence)
---b(4)----------, please comment on whether or not you have tested cross-reactivity with BDD-rFVIII.

Response
---b(4)-- ----------

Reviewer Comment
The response is acceptable.

Question 4 (numbered as #14 in the correspondence)
Please provide a representative –b(4)--------- from analysis of polysorbate 20 in the drug product.

Response
The –b(4)----- of analysis of polysorbate 20 in the DP of –b(4)------- was provided. The data show acceptable polysorbate 20 --------b(4)----------.

Reviewer Comment
The response is acceptable.

Question 5 (numbered as #15 in the correspondence)
Please provide a representative –b(4)----- from analysis of rAHF-Fc drug product by –b(4)----.

Response
The representative –b(4)----- of analysis of –b(4)----------) was provided. The data show acceptable rFVIII-Fc ---b(4)----------

Reviewer Comment
The response is acceptable.

Question 6 (numbered as #16 in the correspondence)
Please explain which epitope on FVIII is recognized by the –b(4)----------.

Response
---b(4)-- ----------.

Reviewer Comment
The response is acceptable. –b(4)-- ----------

On April 10, 2014, the following Information Request was sent to Biogen.

Question 7

In the electronic form of the Application, many sections are mistakenly entitled. Please ensure all eCTD module titles for analytical methods and their validation correspond correctly to their content. In particular, please update the eCTD by making the following corrections:

1. Sections 3.2.S.4.2.4 and 3.2.S.4.3.4: the title "—b(4)----------" should be corrected to –b(4)----------
2. Sections 3.2.S.4.2.5 and 3.2.S.4.3.5: the title "Coagulation Assay (aPTT)" should be corrected to "-b(4)---------
3. Sections 3.2.S.4.3.6 and 3.2.P.5.3.11: reference to the Chromogenic Assay as a compendial assay should be removed and replaced by the method validation report.
4. Sections 3.2.P.5.2.9: the title "---b(4)----------)" should be corrected to "—b(4)----------
5. Sections 3.2.P.5.2.10: the title "Coagulation Assay (aPTT)" should be corrected to "—b(4)----------

Reviewer Comment

According to clarification of the chairperson of the review committee, the review can be completed before addressing these issues as the update of the entire electronic file to include all amendments is required prior to approval. Thus, the Reviewer assumes that these concerns will be addressed.

REVIEWER'S COMMENTS

Upon review of the relevant information, I have not identified issues that prevent approval.

CONCLUSION

From a product reviewer's perspective, STN 125487/0 can be approved.